CELL CYCLE CONTROL PART II
Cyclins

M. KARÇAALTINCABA*
M. A. ÖZTÜRK*
W. E. CRISS*

SUMMARY: During the past five years, the important role of cyclin/cdk heterodimers has been discovered. Regulation of G2/M transition by p34cdc2/cyclin B is summarized in Figure 1 . The newly identified cdk genes, together with the emerging large family of cyclins will allow clarification of the molecular interactions in cell cycle control which involve suppressor genes, oncogenes and the true molecular basis of cancer. This information will be extremely valuable in our attempts to control the growth of cancer cells and tissues.

Key Words : Cyclins, cell cycle control, cyclin dependent kinases, oncogenes, suppressor genes.

INTRODUCTION

Cyclins were first characterized by the observation that they increased in abundance during interphase and were rapidly degraded at each meiotic or mitotic division (1). They were originally identified in the eggs of marine invertebrates, but have since been described in a wide variety of organisms including viruses (2,3). In recent years the definition of cyclins has broadened to include any protein that has structural homology to the classical cyclins (A and B) and that binds to cyclin dependent kinases (cdks). Five classes of cyclins (A,B,C,D,E) have been described in human cells (4). The former two are called M cyclins; the remaining three are called G1 cyclins. As a general feature cyclins bind cdks and act as their regulatory subunits. They are thought to regulate both substrate specificity and phosphorylation status of cdks. M (mitotic) cyclins have clearly been shown to determine the substrate specificity (5). Conservation of different cyclins in eukaryotes suggests that each type has independent functions. The general features of cyclins are summarized in Table 1.

The destruction of cyclin A and B during mitosis is mediated by a 'mitotic destruction motif' near the amino terminus of the protein that targets it for ubiquitin dependent degradation (6). Cyclins, C, D and E do not contain such a motif. However all three proteins contain PEST sequences near the carboxyl terminus which suggests that they are target proteins for rapid and constitutive degradation (7,8). The Cln proteins (G1 cyclins of yeast) also contain such sequences near their carboxyl terminals which may cause their metabolic instability (9). Hence cyclins C, D and E may be unstable proteins (8).

Table 1: Methods used to evaluate cyclins.

Cyclin Type	Cell Cycle Stage	Associated Proteins	Protein Levels	Linkage to Cancer?
A	G2-M and S	cdk2, cdc2, E1A E2F, DRFT-1, pRB	transcription/ proteolysis	Hepatocellular carcinoma Complex with E2F isrupted by E1A
B	G2-M	cdc2, cdc25?	transcription/ proteolysis	No
C	G1	cdc2, cdk?	transcription	Not determ.
D	G1-S?	cdc2, cdk2, 3,4,5 PCNA, p21, pRB	transcription	bcl-1 oncogene Combines with E2F Phosphoylate pRB
E	G1, S?	cdc2, cdk	transcription	Probably no

(Modified from reference 2)

* From Department of Biochemistry and Institute of Oncology, Medical School, Hacettepe University, Ankara, Türkiye.

Cyclins C, D and E cDNAs encode predicted proteins of 303, 295 and 396 amino acids (aa), respectively (10). While both cyclins C and D are considerably smaller than cyclins A (432 aa) and B1 (433 aa) (10) Cyclin D and cyclin E are more closely related to A and B type cyclins. Cyclin A and cyclin B mRNAs accumulate throughout the cell cycle in HeLa cells. They peak at the G2/M boundary (2). These patterns correlate well with the timing of the accumulation of the respective proteins in these cells. Both cyclin C and cyclin E mRNA are elevated during G1. Cyclin E mRNA peaks in late G1 near G1/S boundary (8). This timing suggests that cyclin E plays a role in the G1/S boundary or in S phase. Cyclin C is thought to act at the R point.

M CYCLINS

M cyclins levels were seen to peak at each M phase. Two types (A and B), were distinguished in sea clams by different gel mobilities and the slightly earlier appearance and disappearance of cyclin A (11). Cyclin A and cyclin B mRNAs induce entry into mitosis in Xenopus eggs (12). Similarities among the cyclins from different cell species is restricted to an internal region of approximately 150 amino acid residues which is called the cyclin box (13-15).

CYCLIN B

The first isolated and most studied is cyclin B. It is found to have a role in the control of the entry into mitosis. Cyclin B accumulates during interphase and associates exclusively with cdk1 among cdks. The formation of this complex was accompanied by phosphorylation of the threonine residue 161 and subsequent activation of cdk1. Two cyclins were identified in humans, B1 and B2 (16). There is some similarity between protein tyrosine phosphatases and each of the classes of cyclin. Whereas only B type cyclins activate cdc25. The similarity is greatest between B class of cyclins and protein tyrosine phosphatases. This might be related to specific ability of cyclin B but not A, C, E or D type cyclins to activate cdc25 (17). Cyclin B was also shown to determine the intracellular localization of cdk1 (18). Cyclin B was degraded at the end of metaphase (19), but in a recent paper it was reported that cyclin B degradation allowed the exit from mitosis rather than entry into anaphase in yeasts (20). In contrast, cyclin B, but not cyclin A has been reported to inhibit membrane fusion in vitro (21).

CYCLIN A

Cyclin A also accumulates during interphase in the cytoplasm of cellularized embryos, but moved to the nuclear region early in prophase and was completely degraded within metaphase (22). Cyclin A was expressed in dividing cells throughout development, and a functional cyclin A gene was required for continued division after exhaustion of maternally contributed cyclin A during the embryo genesis of drosophila (23). Cyclin A was found in mammalian tissue culture cells in a complex with cdk2 (24,25). This complex was activated at the G1/S transition and was found in the cell nucleous throughout the S phase (24). This complex has also been found in a larger complex containing the product of retinoblastoma gene pRB (or the related p107) and the transcription factor E2F. The latter was released from this complex when the adenoviral oncoprotein E1A was expressed (25).

Recently direct evidence for the involvement of cyclin A in the regulation of S phase has been obtained. Antibodies against cyclin A or anti-sense plasmids inhibited entry into S phase if injected into tissue culture cells during G1 phase (26). Observations in drosophila and Xenopus oocytes, on the other hand suggested that cyclin A was not essential for entry into the S phase. In Xenopus egg extracts, cell cycle progression did not seem to require cyclin A, although cdk2 was clearly required for the S phase (27). Differences in the regulation of entry into S phase in the growth independent and the growth regulated, later cycles with G1 phases are expected and might explain these contrasting observations. Therefore there is the probability of cyclin A being a substrate of putative S phase Promoting Factor (SPF) as S cyclin (Figure 1).

Cyclin A was found not only in association with the cdk2, but also in a complex with p34cdc2 kinase. Cyclin A/p34cdc2 and cyclin B/p34cdc2 have similar but not identical properties in vitro. The cyclin A/p34cdc2 complex was not efficiently phosphorylated on Tyrosine 15 and was therefore activated more rapidly than cyclin B/p34cdc2 complex (28). Moreover, these two complexes had different actions on microtubule dynamics and endosome fusion (29). Thus the cyclin A/p34cdc2 complex has been suggested to act as starter kinase regulating prophase events and the activation of cyclin B/34cdc2 complex may control proceeding events (30). Also cyclin A and cyclin B act synergistically to facilitate the organization of the mitotic

spindle and allow a rapid progression through mitosis (31). Cyclin A was implicated in the dependence of mitosis upon the completion of DNA replication (32).

In addition, the hepatitis B virus was shown to integrate into a cyclin gene in a hepatocellular carcinoma (33). As cyclin A is important in the control of S and M phases, this activation by a virus might contribute to tumorigenesis.

G1 CYCLINS

The genes encoding cyclin C, cyclin D and cyclin E were discovered by screening human and drosophila cDNA libraries for genes that could complement mutations in the Saccharomyces cerevisae CLN genes, that encode G1 cyclins (8-10).

CYCLIN C

Cyclin C also associates with p34cdc2 (9). The distant relationship of cyclin C to the other members of the cyclin family may not be the result of rapid evolutionary divergence of this cyclin. Cyclin C conservation from drosophila to human (72% identity) is much higher than the conservation of other cyclins (e.g. 31% identity between human and drosophila cyclin A). This suggests that cyclin C has important functions that severely constrain evolutionary divergence. Cyclin C appears to be a diverged cyclin homology and does not appear to belong to any of the cyclin subfamilies. Cyclin C mRNA was shown to be synthesized during G1 and accumulated through G1, implicating a role for cyclin C in late G1 (8). Probably it is a key factor in cell size control.

CYCLIN D

The cyclin D gene was first discovered by Motokura *et. al.* as the PRAD 1 oncogene (34). Later it was called bcl-1 oncogene by the same group (35). Three types of cyclin D have been defined in human cells. Cyclin D1, D2 and D3 were assigned to chromosomes 11q13, 12p13, 6p21 respectively (36). Cyclin D was associated with p34cdc2, cdk2, cdk3, cdk4, cdk5 (35,37). In addition cyclin D has been recently shown to phosphorylate pRB fusion protein in vitro in a complex with cdk4 which subsequently caused dissociation of E2F from pRB (38).

In parathyroid adenoma and chronic lymphocytic leukemias, the bcl-1 gene has been found to be near the breakpoints of translocations involving the long arm of human chromosome 11, implying that its unregulated expression might contribute to aberrant growth. Cyclin D was also reported to be involved in centrocytic lymphoma (39). In addition, cyclin D and its homologues were also implicated in breast carcinoma, squamus cell carcinoma and acute myelocytic leukemia (40,41). It was found to be highly expressed in gastrointestinal cancers, especially in esophageal and gastric carcinomas (42,43).

All of these exciting data indicate that cyclin D may be a common point in signal transduction since it is expressed in various cancer types. Being a common point in mitogenic signal transduction could also effect DNA replication. In one recent study, cyclin D was purified from a complex containing certain DNA replication elements such as PCNA (delta subunit of DNA polymerase) and p21 (38).

CYCLIN E

Cyclin E is the third G1 cyclin. Cyclin E mRNA fluctuates throughout the cell cycle. It is maximal near the G1/S boundary (8). These properties indicate that cyclin E might regulate the G1 to S phase transition in human cells. In support of a G1 function for cyclin E, it was shown to bind and activate p34cdc2 kinase in extracts from human G1 cells (10). Later cyclin E was also shown to interact with cdk2 (44,45). The latter complex is maximal in G1 cells (45).

At least two forms of endogenous cyclin E protein were detected in proliferating fibroblasts at 50 and d 55 kd. The 50 kd form was maximally expressed during the late G1 and early S phase. It was induced during mitogenic activation of primary human T lymphocytes (46). In the previous study, it was also observed that cell populations constitutively expressing cyclin E also showed a decreased number of cells in G1 and an increased number in the S phase. This change in cell cycle distribution was consistent with the accelerated transit through G1. So far accumulation of only two proteins, myc protein (47) and cyclin E have been shown to determine the rate of G1 transit. Although many proteins are necessary for entry into S phase.

In addition, when cyclin E was over expressed it was observed to decrease cell size and to diminish the serum requirement for the transition from G1 to S phase (46). However this over expression did not immortalize the cells.

SIGNAL TRANSDUCTION AND CYCLINS

Cyclins, especially the G1 cyclins, are thought to act in the signal transduction of serum growth factor. These molecules may be on of the limiting proteins in the signal transduction of growth factors. A family of cyclin genes, regulated by colony stimulating factor 1 (CSF-1 OR M-CSF) in murine macrophages during G1, may represent targets of growth factor action that are necessary for entry into the S phase (48). In murine macrophages at least two cyclin genes were expressed, CYL1 and CYL2 (cognate cyclin D analogue). These were observed to act at the G1/S boundary. They were degraded during S phase. This was the first time cyclins were shown to act in the signal transduction of a growth factor (48,49).

In addition, the G1 cyclins of Saccharomyces cerevisae are speculated to act downstream in G protein mediated mitogenic signal transduction pathway (50). Recently cyclin A was observed to be common key downstream target along certain induced (INF, IL-6,TNF-beta) growth suppressive pathways (51). Also there is a structural similarity between cyclins and ras oncogene protein (9) which may be an important element of signal transduction.

GROWTH CONTROL AND CELL CYCLE CONTROL

In cell cycle studies it has been difficult to identify the specific gene functions required for cell cycle commitment in G1. However yeast cells are very useful for this purpose because they form mutants that exhibit a cell division cycle (cdc2) phenotype, that is to say they continue to grow while some features of the nuclear division cycle are blocked. Cell growth and cell cycle are intimately related, but the detailed picture of the way that these two processes are coordinated is not understood. Probably cyclins are the common point of both processes. G1 cyclins have been reported to regulate cell size, and it is known that these cyclins complex with cdks and regulate the cell cycle.

Negative controls over cell proliferation which may be operating in vivo are increasingly the focus of experimental attention. The cellular components of the mechanisms that negatively control proliferation include products of tumor suppressor genes, such as p105Rb and p53 (52). Whether these gene products act principally to suppress cell growth or to block cell cycle progression has to be established.

CANCER RELATED GENES AND CELL CYCLE CONTROL

Cancer related genes products are thought to play role in different parts of the cell cycle. The site of actions of the cancer related genes are documented below.

G0/G1 BOUNDARY

Several genes have been involved in G0-G1 transition. V-sis and K-fgf/hst, encoding a PDGF beta-like protein (53) and fibroblast growth factor, respectively, act in this stage by enhancing progression through G1.

c-fos and c-jun, as immediate early genes, interact with genomic sites containing an Activator Protein 1 (AP1) sequence. They function as homo or heterodimers through a leucine zipper binding mechanism (54). Thus they may produce a large number of different cellular signals and permit a level of sophisticated control during transcription.

Increased expression of c-myc occurs early after stimulation of quiescent cells and does not require protein synthesis, so it is also considered as immediate-early growth gene (53).

Oncogene involvement in the mitogenic stimulation of quiescent cells directly involves the expression of genes which are quiescence specific (e.g. p20k), (55). It is conceivable that the relationship to oncogenes, probably an inhibitory effect, will be found for one or more genes in this group. Furthermore the action of oncogenes on G1 progression is extremely complex and probably requires a complex interaction of several oncogenes.

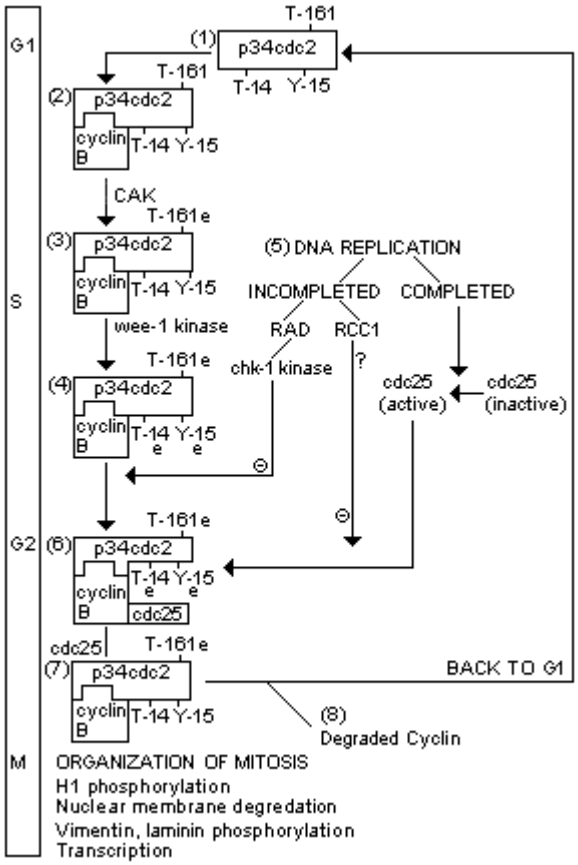
G1 TO S TRANSITION

Up-regulation of the genes of the ras family is seen by following growth induction of quiescent cells. Because it occurs later than c-fos, c-jun or c-myc (56). It is probably required for the G1-S transition 'downstream' of serum factors and the primary responder gene products (53).

The G1-S transition may also be the target of proteins encoded by oncogenes carried by DNA viruses. SV40 virus facilitates the entry of human lung cells into the S phase. These cells express the large T antigen which forms an oligomeric complex with a cellular phosphoprotein p53 (53). This is the protein product of p53 cancer suppressor gene. Unaltered p53 has growth suppressive properties (57). Also the

Figure 1: Proposed mechanism for regulation G2/M transition by MPF.

1. Inactive p34cdc2 accumulates in G1.
2. Transient association with cyclin B causes a conformational change that exposes residues Thr 14 (T14), Thr 15 (Y15) and Thr 161 (T161) to various kinases.
3. Phosphorylation of T161 by CAK stabilizes association with cyclin B.
4. Phosphorylation of T14 and Y15 by wee-1 enables MPF to accumulate as inactive complex.
5. Inactive DNA replication is completed, MPF is activated by cdc25.
6. cdc25 binds with cyclin B and dephosphorylates p34cdc2 at T14 and Y15, thus activates MPF.
7. Active complex regulates mitosis.
8. Degradation of cyclin B by ubiquitin-dependant pathway allows cell to exit from mitosis.



retinoblastoma protein (protein product of a cancer suppressor gene-Rb) acts in this stage as a suppressor of tumorigenesis.

G2 TO M PHASE TRANSITION

The most important molecule for the G2-M phase transition in MPF. It is becoming clear that MPF is phosphorylated by certain oncogene products. pp60-src was shown to phosphorylate MPF in vitro (52). Another oncogene (v-mos) product activated MPF during meiosis (58). Also the c-ras oncogene protein may act on MPF directly or indirectly (59). There are other oncogene proteins which are phosphorylated at the M phase as c-abl, c-myc, c-myb (59). The mechanism as to how these oncogene products act on MPF, and how MPF acts on the oncogene products is not clear, but it is obvious that phosphorylation is very important for the regulation of MPF.

Cyclins, which form heterodimers with cdks are of key importance. They may be very important in neoplastic transformation. In this regard cyclin D and cyclin A are highly suspected to have oncogenic potential.

CANCER AND CELL CYCLE CONTROL

Tumor cells in general have high and uncontrollable proliferation capacity. Since cell proliferation requires the coordination of cytoplasmic growth, DNA replication and cell division, tumor cells must still rely on the cell cycle program. However 'defects' may be present. An unlimited proliferation capacity can be obtained by the constitutive activation of the control program. For example, this could occur through the constitutive expression of cyclins. New cyclins which are implicated in different cancers are being discovered each year. The first cyclin implicated in oncogenesis was cyclin A, which was thought to play a role in hepatocellular carcinoma (33). The second cyclin was cyclin D which has been shown to act in several cancers. It is coded from the bcl-1 oncogene. Recently, it was reported to correlate with oncogenesis in parathyroid adenoma, B cell neoplasms, breast squamous cell cancers, gastrointestinal cancers (40) and acute myelocytic leukemia (41).

Chromosomal instability is a characteristic of cancer cells. Therefore, Neiman and Hartwell have proposed that malignant cells may be those which have lost the mitotic checkpoint control (60). The selective loss of some S and M phase checkpoints may not cause cell death but may contribute to error-prone DNA replication and the propagation of these errors to the daughter cells. Thus, a 'malignant cell cycle' may be defined as one which generates and accumulates selected genetic mistakes. Each division of a malignant cell cycle could lead to a mutagenic event which contributes to the progression of the malignant phenotypes via increased loss of cell cycle control checkpoints.

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Correspondence:
Musturay Karçaaltincaba,
Department of Biochemistry and
Institute of Oncology,
Hacettepe University,
Medical School,
Ankara, TÜRKIYE.43400 UPM
MALAYSIA.